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Effect of oral cephalexin in the treatment of BCG lymphadenitis

Effetti di cefalexina orale per il trattamento della linfadentite da BCG

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INTRODUCTION

Lymphadenitis and abscess formation are the most common side effects of Bacille Calmette-Guerin (BCG) vaccination. The incidence of BCG lymphadenitis differs worldwide, ranging from 0.5% to 23%. The likelihood of lymphadenitis is higher when BCG vaccination is performed at a lower age [1-12]. Tuberculosis (TB) remains a global public health problem and is considered a vital health issue in countries with low income, poor nutrition, and unmodified social standards [4].

The BCG vaccine, which is used to prevent TB, has been made available to the public since 1921. The World Health Organization (WHO) offers BCG vaccination as part of the Global Expanded Program of Immunization (EPI) in developing countries [5, 13]. The BCG vaccine is a live attenuated vaccine that was developed from a strain of *Mycobacterium bovis* [5]. Its efficacy has been reported to vary from 50% to 90% [12, 14, 15]. Although its efficacy is not considerable, some studies report that the BCG vaccine can prevent miliary TB and tuberculous meningitis [16].

After intradermal injection of the TB vaccine, BCG begins to proliferate at the injection site and then infiltrates the regional lymph nodes through the lymphatic system. Finally, it is carried away by the blood and forms small foci of infection in various organs. This sequence of events is the normal BCG reaction, which results in successful BCG vaccination [17].

Although BCG vaccination is safe, it can occasionally cause lymphadenitis, localized ulceration, osteomyelitis, lipoid reactions, eczema vaccinatum, hypertrophic scars, keloid formation, disseminated infection, and death [4, 5, 14, 15, 18-21].

Two forms of BCG lymphadenitis may occur after TB vaccination. The first is a simple, nonsuppurative lymphadenitis, which resolves spontaneously in a few weeks. The second form is a suppurative lymphadenitis, which is characterized by a fluctuant swelling, erythema, and edema of the skin [4, 5].

Opinions on how to treat the acute symptoms vary widely and include many types of interventions such as surgical drainage, antibiotics, and even anti-TB treatments. The usefulness of these treatments is controversial [5, 15, 18]. The present study investigated the effect of oral cephalexin on patients who developed BCG lymphadenitis after anti-TB vaccination.

PATIENTS AND METHODS

The study involved 40 children (24 boys and 16 girls) who were referred to Qazvin Chil-

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dren's Hospital, Qazvin, Iran, for the treatment of non-suppurative BCG lymphadenitis between December 2008 and the end of September 2009. Qazvin Children's Hospital is a referral center in which about 10,000 children are hospitalized in a year, and 100,000 children are treated in its outpatient clinics every year. It covers not only patients from Qazvin province but also some patients from neighboring provinces. The diagnostic criteria for BCG lymphadenitis consisted of ipsilateral axillary, supraclavicular, or cervical lymphadenitis, with the affected nodes measuring at least 0.5 cm wide, and the absence of any detectable cause other than BCG vaccination administered up to 6 months before. The inclusion criteria for this study were:

1) age below 36 months;
2) BCG lymphadenitis;
3) no other diseases, and
4) no history of any treatment prior to admission [1].

In total, 40 children who met the above criteria were included in the study after obtaining the approval of the hospital ethics committee and consent from the children's parents.

All patients were examined by a pediatric infectious disease specialist. The size of the lymph nodes and the BCG scar was noted. The largest transverse diameter of the affected lymph nodes was recorded as the lymph node size. All patients had received 0.05 ml (0.05 mg) BCG vaccine (Pasteur Institute, Tehran, Iran) intradermally in the distal third of the deltoid muscle of the right arm [1, 4].

To our knowledge, the susceptibility of *Mycobacterium bovis* to cephalexin has not been evaluated. This antibiotic was selected because (1) it is active against gram positive organisms such as *Staphylococcus aureus*, which may complicate BCG lymphadenitis, and (2) a literature review indicated that most staphylococcal infections are susceptible to cephalexin. Thus, this antibiotic would treat superimposed bacterial infection, which is likely to complicate BCG lymphadenitis. Patients were randomly divided into two groups A and B. Patients in group A (n = 20) did not receive any treatment and were considered as the control group. Group B patients received oral cephalexin (50 mg/kg/day in four doses) for 10 days. If the affected lymph nodes were fluctuant in the follow-up period, fine needle aspiration (FNA) was performed [1]. To prevent sinus formation, FNA was performed by inserting the needle 2 cm away from the periphery of the lymph nodes [1].

All patients were called to the hospital for re-examination 10 days after the last cephalexin dose was administrated. During re-examination, each patient underwent a complete physical examination, and the lymph node size and local symptoms such as fluctuation, warmth, and erythema as well as systemic symptoms were noted.

Serial examinations continued until recovery from lymphadenitis, which was defined as a decrease in lymph node size to <0.5 cm and the absence of local symptoms such as sinus formation and residual ulceration, without any systemic symptoms or radiographic changes indicative of tuberculosis.

Data from the two groups were compared by the unpaired student T test. The alpha coefficient was taken as 0.05.

RESULTS

In all 40 patients who met the inclusion criteria, the findings of clinical examination were normal, except for lymphadenitis. The mean age at onset of lymphadenitis in the patient (A) and control (B) groups was 5.5±2.87 and 6.07±3.35 months, respectively (Table 1).

The axillary lymph nodes were involved in 38 patients (19 each in the intervention and control groups), and the supraclavicular lymph nodes were involved in 2 patients (one each in the intervention and control groups).

A polymerase chain reaction (PCR) test was performed in both groups and was positive for TB bacilli. FNA had to be performed in 3 patients in the control group and 2 patients in

Table 1 - Clinical findings in both groups.

	Number	*Mean age at onset of lymphadenitis (months)*	*Lymphadenitis size*		
			<1 cm	*1-3 cm*	*<3 cm*
No treatment	20	6.07±3.35	7	9	4
Cephalexin	20	5.5±2.87	7	10	3

the intervention group because of the emergence of lymphadenitis complications.
The average recovery period in the intervention group (16.1±6.5 weeks) was similar to that in the control group (15.8±5.7 weeks). None of the patients experienced side effects of cephalexin during the study.

DISCUSSION

After intradermal injection of the BCG vaccine, the vaccine intervention spreads through the lymphatic system to the local lymph nodes and induces immunity against primary tuberculosis infection. However, the level of immunity provided against the various forms of tuberculosis differs [5, 6, 22]. BCG vaccination leads to the formation of the classic primary complex, which consists of a cutaneous nodule at the vaccination site and swelling of the local lymph nodes. This phenomenon is usually self-limiting and requires no treatment [1, 5]. However, a small percentage of these patients develop an excessive reaction that eventually progress to suppurative lymphadenitis [1, 5, 22]. BCG lymphadenitis usually occurs 2 to 8 weeks after vaccination; however, some studies have reported the emergence of BCG lymphadenitis after 8 months [5, 14, 15, 23, 24]. Factors influencing the incidence of BCG lymphadenitis include vaccination technique, vaccine type, age, dose, concentration, potency, viability, immunogenicity, prior exposure to mycobacterial antigen, and duration of vaccine storage [1, 5, 14, 15, 23-26]. Vaccination at a lower age is associated with a higher possibility of subsequent BCG lymphadenitis. Studies on children with BCG lymphadenitis have shown that malnutrition and immune deficiency do not considerably affect the development of BCG lymphadenitis [1,5].
An epidemic of BCG lymphadenitis has been reported in many countries, including Iran [5, 14, 27-33]. Analysis of these epidemics has shown that BCG lymphadenitis constitutes a strong response to potent, highly safe vaccines. BCG vaccines are produced in various laboratories, and thus, the BCG strains used differ slightly with regard to phenotype and genotype [5, 14, 21]. The vaccines prepared from these strains probably differ in terms of their side effects and protective effects [14].
Treatment strategies for BCG lymphadenitis range from no intervention to various medical and surgical treatments [17, 28, 34-40]. Erythromycin was the first drug reported to be effective against ulcers and abscesses that form after BCG vaccination and to accelerate the recovery process [41]. However, randomized controlled trials have found that erythromycin is ineffective for the treatment of BCG lymphadenitis [1, 42, 43]. The findings of these trials are probably correct because the minimum inhibitory concentration (MIC) of erythromycin against tuberculous bacilli is much higher than blood and tissue concentrations after oral erythromycin administration [41].
Oguz and Caglayan found that erythromycin may have some beneficial effect on lymphadenitis that occurs soon after BCG vaccination, but erythromycin is not routinely prescribed for the treatment of BCG lymphadenitis [40, 42]. Kuyucu et al. found that the mean recovery time in patients treated by aspiration and oral erythromycin administration was identical to that in patients who received no treatment [1]. Some authors have reported that because of the effect of erythromycin on gram-positive cocci, the administration of this drug tends to complicate BCG lymphadenitis [43].
Furthermore, Baki et al. showed that while isoniazid (INH) administration does not decrease disease duration, surgical intervention effectively shortens the duration of BCG lymphadenitis [17]. Since BCG bacilli are susceptible to INH, the ineffectiveness of this drug in the treatment of BCG lymphadenitis is surprising and intriguing [6]. One possible explanation could be an underlying hypersensitivity response to BCG proteins as well as to INH and other anti-TB drugs [37]. Another explanation is that the BCG bacillus plays no role in the formation of BCG lymphadenitis; samples from affected lymph nodes show low positivity for bacilli on culture, and few acid-fast bacilli (AFB) are present in smears prepared from such lymph nodes [27, 43].
During treatment of tuberculous lymphadenitis, hypersensitivity responses, characterized by enlargement, fluctuant swelling, and suppuration of the lymph nodes, can occur, and these responses are similar to the clinical course of BCG lymphadenitis treated with INH [44].
In a study conducted by Bhandari on 40 children, recovery from BCG lymphadenitis was

faster after surgical intervention than after drug treatment alone [45]. Furthermore, in that study, treatment with INH or streptomycin or both was administered to 26 patients with BCG lymphadenitis, but none of the treatments shortened the recovery period [45]. Other authors found that AFB were detected in more than a third of the patients in their study; however, Bhandari reported that AFB were not detected on direct smear in any of their study patients [45-47].

In our study, PCR tests demonstrated the presence of TB bacilli in all patients. In the study by Bhandari, as in many other studies, recovery from non-suppurative adenitis occurred within 12-15 weeks. Bhandari did not find a statistically significant reduction in the time until recovery from BCG lymphadenitis by various treatment regimens such as erythromycin, INH, INH plus erythromycin, and placebo (P>0.05) [45].

In the current study, treatment with oral cephalexin did not hasten recovery from BCG lymphadenitis (P>0.05). Mehta et al. have shown that anti-TB drugs are useful for the treatment of BCG lymphadenitis [48]. However, Bhandari et al. reported that anti-TB drugs have no therapeutic effect on BCG lymphadenitis [45]. In our study, we found that cephalexin has no effect on BCG lymphadenitis.

CONCLUSION

Our study and recent research show that non-suppurative lymphadenitis after BCG vaccination is a benign condition that usually improves spontaneously within 3 to 4 months. In such cases, it is sufficient to simply reassure the parents. If lymphadenitis is purulent, the most appropriate treatment is surgical drainage of the lymph nodes and antibiotic therapy.

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Keywords: BCG, lymphadenitis, cephalexin, PCR, needle aspiration.

SUMMARY

Lymphadenitis and abscess formation are the most common side effects of vaccination with Bacille Calmette Guerin (BCG).

The lower the child's age at the time of vaccination, the higher the incidence of BCG lymphadenitis tends to be. Although various therapeutic approaches are in use for the treatment of BCG lymphadenitis, there is no consensus on which of them is optimal.

This study aimed to determine whether oral cephalexin treatment hastens recovery from BCG lymphadenitis.

The study involved 40 children (24 boys and 16 girls) with BCG lymphadenitis who were referred to Qazvin Children's Hospital, Qazvin University of Medical Sciences between December 2008 and the end of September 2009. The patients were randomly assigned to two groups of 20 patients each (12 boys and 8 girls in each group): group A patients did not receive any treatment and served as controls, and group B patients were treated with 50 mg/kg/day cephalexin syrup, administered in four doses, for 10 days.

In all patients, clinical examination was normal, except for lymphadenitis. In all patients, BCG vaccination had been performed at birth, and polymerase chain reaction tests were positive for tuberculous bacilli. The recovery period and requirement of fine needle aspiration did not significantly differ between the two groups (P > 0.05). This study showed that treatment with cephalexin does not hasten recovery from BCG lymphadenitis.

RIASSUNTO

La linfadenite e la comparsa di ascessi sono gli effetti collaterali che si verificano con maggiore frequenza in seguito alla vaccinazione con i bacilli di Calmette Guerin (BCG). L'incidenza della linfadenite da BCG è tanto maggiore quanto minore è l'età del bambino al momento della vaccinazione. Per il trattamento della linfadenite da BCG, sono in uso diversi approcci terapeutici ma non vi è un consenso unanime su quale di essi sia da ritenere ottimale.

Questo studio è stato intrapreso al fine di determinare se il trattamento con cefalexina per via orale sia in grado di accelerare il processo di guarigione dalla linfadenite da BCG.

Nello studio sono stati arruolati 40 bambini (24 maschi e 16 femmine) affetti da linfadenite da BCG inviati al Qazvin Children's Hospital, Qazvin University of Medical Sciences nel periodo dicembre 2008 - fine settembre 2009.

I pazienti sono stati randomizzati in due gruppi di 20 pazienti ciascuno (12 maschi e 8 femmine in ciascun gruppo): i pazienti del gruppo A non hanno ricevuto nessun trattamento e sono stati utilizzati come controlli mentre i pazienti del gruppo B sono stati trattati con 50 mg/kg/die di cefalexina sciroppo, somministrato in quattro dosi per 10 giorni. In tutti i pazienti, l'esame clinico è risultato normale, fatta eccezione per la presenza di linfadenite. In tutti i pazienti, la vaccinazione con BCG era stata effettuata alla nascita e i test con la polymerase chain reaction *sono risultati positivi per la presenza di bacilli tubercolari. Il periodo di guarigione e la necessità di ricorrere ad aspirazione con ago sottile non differivano tra i due gruppi in maniera significativa (P > 0,05). Il nostro studio ha indicato che il trattamento con cefalexina non accelera la guarigione della linfadenite da BCG.*

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